

EDITORIAL COMMENT

Allergic Reactions After the Implantation of Drug-Eluting Stents

Is it the Pill or the Polymer?*

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Drug-eluting stents (DES) have been demonstrated to decrease clinical and angiographic restenosis rates compared to bare-metal stents (1,2). Their use continues to increase and now accounts for >75% of all stents utilized; more than 2,000,000 DES have been implanted in the U.S. to date (3,4). In this issue of the *Journal*, Nebeker et al. (5) report on hypersensitivity cases associated with implantation of DES from the Research on Adverse Drug/Device Events and Reports (RADAR) (6). Despite several important limitations including those inherent to the analysis of post-marketing surveillance data, the report represents the largest and most ambitious analysis of hypersensitivity reactions to DES published. A concerted attempt has been made to delineate the cause, clinical course, and sequelae of hypersensitivity reactions after DES implantation.

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Data for the study were obtained from the Food and Drug Administration's (FDA) Manufacturer and User Device Experience Center (MAUDE) (7), but the authors also utilized data obtained from a review of electronic databases and their own clinical practice. A total of 262 cases of hypersensitivity reactions associated with DES implantation were evaluated to assess the etiology as well as the severity.

On the basis of available information, 17 of 262 cases (14 CYPHER [Cordis Corp., Miami Lakes, Florida] and 3 TAXUS [Boston Scientific Corp., Natick, Massachusetts]) were classified as probably or certainly caused by the stent implantation. Four autopsies in patients who died of coronary thrombosis confirmed intrastent eosinophilic inflammation, thrombosis, and lack of intimal healing; 13 cases were classified as "probably" having a hypersensitivity reaction to DES (8). Clinical manifestations were primarily cutaneous, usually beginning within 10 days of stent implantation. Symptom duration was >4 weeks in 11 of 17 patients.

Based on the findings of the autopsy studies, one can conclude that hypersensitivity to DES is a real entity. The authors have shown that when present, hypersensitivity reactions after DES can result in serious clinical sequelae, including need for hospitalization (18%), emergent interventions such as intravenous steroids or repeat catheterization (34%), or death (2%). However, determination of the incidence and overall clinical significance of hypersensitivity reactions after DES implantation is more problematic.

There are several important limitations of this study, including those pertaining to the use of the FDA's MAUDE center. First, the true incidence of the event cannot be reliably estimated. These events are primarily self-reported either by the manufacturer or health care personnel. While adverse post-marketing events are generally underreported to the FDA (9), the magnitude of underreporting is unknown for any given device or medication. Adverse event reports require only the suspicion of a relationship to the device or medication and do not imply causality. The clinical information may be incomplete in many instances. In the study, concomitant medications were not reported 40% of the time, and the de-challenge response to medications was not reported in 81% of cases. Although the authors made an attempt to ascertain the cause of the hypersensitivity reaction, an unequivocal cause and effect could be proven in only four cases.

Finally, the denominator is unknown. Although the number of stents implanted is available, the exact number of patients who have undergone DES implantation is unknown. However, even assuming two DES are placed per patient, the incidence would still be extremely low (0.002%).

Nevertheless, post-marketing analysis of adverse events has many advantages. Pre-marketing clinical trials typically enroll <5,000 patients and are not powered to detect rare adverse events (10); post-marketing analysis can detect these rare events (11). Also, after marketing, many medications and devices are used in a broader, higher-risk population that was not included in the pre-marketing studies. Post-marketing adverse event reporting has contributed to the withdrawal of several medications (12).

In patients with documented hypersensitivity reactions after DES implantation, the reaction could be due either to medical therapy associated with stent implantation or to the DES itself. Several components of the DES could be responsible for the hypersensitivity reaction. These include the polymer coating, the drug (rapamycin for CYPHER and paclitaxel for TAXUS), or the stent itself. The use of bare-metal stents has not been associated with hypersensitivity reactions. A series of >400 autopsies revealed no evidence of hypersensitivity reactions to the bare-metal stent (13). Drug reactions to rapamycin are extremely uncommon (14). Paclitaxel has been associated with hypersensitivity reactions, but many of these reactions have been attributed to the castor oil vehicle (15). Thus, the most likely etiology of the hypersensitivity reaction is the polymer coating of the

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DES. Related synthetic polymers, when applied to bare-metal stents, have demonstrated both local and systemic hypersensitivity responses after implantation in one animal study (16).

Patients with known coronary artery disease who have undergone implantation of DES typically require multiple medications. Determining the cause of a hypersensitivity reaction is often confounded by the potential for hypersensitivity to concomitant medications. Of particular importance for the clinician is the hypersensitivity reaction to the commonly prescribed thienopyridine antiplatelet agent clopidogrel, which occurs in 5% of patients (14). The most common presentation is rash; more serious hypersensitivity reactions requiring treatment with corticosteroids are rare (17). Clopidogrel desensitization has been accomplished successfully in one case report and is an option in patients with prior reactions (18). Alternatively, one could utilize ticlopidine. However, use of ticlopidine is associated with higher rates of adverse reactions, including thrombotic thrombocytopenic purpura and neutropenia.

It is important to not terminate thienopyridine therapy early after stent implantation in patients with a suspected hypersensitivity reaction as this has been associated with stent thrombosis (19,20). In a recent study, stent thrombosis occurred in 29% of patients in whom antiplatelet therapy was prematurely discontinued (20). On the other hand, continuation of the offending agent in the presence of a serious allergic reaction can also be dangerous.

In summary, hypersensitivity to DES is a real entity and can result in serious clinical sequelae including stent thrombosis and death. While the exact incidence is unknown, it appears to be extremely low based on available data. Clinicians should be familiar with the clinical presentation of these hypersensitivity reactions, and any suspected patient with a potential hypersensitivity reaction after DES implantation should be evaluated thoroughly and monitored closely; failure to do so can result in serious clinical consequences. Continued surveillance of hypersensitivity reactions after DES implantation is an important process and should further enhance our current understanding of this entity.

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REFERENCES

1. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003;349:1315-23.
2. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004;350:221-31.
3. Mueller T. Stories of Survival and Hope Mark the One Million Patient Milestone for the CYPHER Sirolimus-Eluting Coronary Stent. Miami Lakes, FL: COMTEX, 2005.
4. Boston Scientific Announces Implantation of Millionth TAXUS Express2 Coronary Stent System. Natick, MA: Boston Scientific Corporation, 2005.
5. Nebeker JR, Virmani R, Bennett CL, et al. Hypersensitivity cases associated with drug-eluting coronary stents: a review of the available cases from the Research on Adverse Drug Events and Reports (RADAR) project. *J Am Coll Cardiol* 2006;47:175-81.
6. Bennett CL, Nebeker JR, Lyons EA, et al. The Research on Adverse Drug Events and Reports (RADAR) project. *JAMA* 2005;293:2131-40.
7. Manufacturer and User Facility Device Experience Database. Rockville, MD: Food and Drug Administration 2004.
8. Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. *Ann Intern Med* 2004;140:795-801.
9. Ahmad SR. Adverse drug event monitoring at the Food and Drug Administration. *J Gen Intern Med* 2003;18:57-60.
10. Beran RG. The ethics of post-marketing surveillance of therapeutic agents. *Med Law* 2001;20:587-94.
11. Meyboom RH, Egberts AC, Edwards IR, Hekster YA, de Koning FH, Gribnau FW. Principles of signal detection in pharmacovigilance. *Drug Saf* 1997;16:355-65.
12. Wysowski DK, Swartz L. Adverse drug event surveillance and drug withdrawals in the United States, 1969-2002: the importance of reporting suspected reactions. *Arch Intern Med* 2005;165:1363-9.
13. Virmani R, Guagliumi G, Farb A, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation* 2004;109:701-5.
14. Mosby's Drug Consult. St. Louis, MO: Elsevier Inc., 2004.
15. Rowinsky EK, Donehower RC. Paclitaxel (taxol). *N Engl J Med* 1995;332:1004-14.
16. van der Giessen WJ, Lincoff AM, Schwartz RS, et al. Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. *Circulation* 1996;94:1690-7.
17. Fischer TC, Worm M, Groneberg DA. Clopidogrel-associated angioedema. *Am J Med* 2003;114:77-8.
18. Camara MG, Almeda FQ. Clopidogrel (plavix) desensitization: a case series. *Catheter Cardiovasc Interv* 2005;65:525-7.
19. McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet* 2004;364:1519-21.
20. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005;293:2126-30.